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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,320	11/03/2005	Yoshiko Takayama	2005_1592A	1755

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EXAMINER	
HUANG, GIGI GEORGIANA	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
08/16/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)
	10/553,320	TAKAYAMA ET AL.
	Examiner	Art Unit
	GIGI HUANG	1627

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-16 and 18-20* is/are pending in the application.

4a) Of the above claim(s) *14-16, 18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 5, 2011 has been entered.

Status of Application

2. The response filed July 5, 2011 has been received, entered and carefully considered. The response presents arguments and declaration which are addressed below.

3. Claims 13-16, 18-20 are pending in the case.

4. Claim 13 is present for examination.

5. All grounds not addressed in the action are withdrawn or moot due to arguments and affidavits.

6. New grounds of rejection are set forth in the current office action.

Grounds of Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hellberg et al. (WO 03/020281) in view of McKerracher et al. (WO 99/23113), McKerracher (Ganglioside rafts as MAG receptors that mediate blockade of axon growth), and Hara et al. (Protein kinase inhibition by fasudil hydrochloride promotes neurological recovery after spinal cord injury in rats).

The claim is directed to a method of promoting neuritogenesis of the cornea, which was damaged by cornea surgery/disease, with the administration of a ROCK (rho kinase) inhibitor from the group consisting of 2-chloro-6,7-dimethoxy-N-[5-1H-indazolyl]quinazoline-4-amine, N-(1-benzyl-4-piperidinyl)-IH-indazole-5-amine dihydrochloride, 4-[2-(2,3,4,5,6- pentafluorophenyl)acryloyl]cinnamic acid and fasudil hydrochloride.

Rejection:

Hellberg et al. teaches the use of compounds that promote neuron regeneration or neurite outgrowth (both neuritogenesis), for the treatment of conditions from injury (damage) to the corneal nerve such as after surgeries or trauma, including dry eye and other conditions related to corneal nerve damage (e.g. corneal sensitivity after LASIK) encompassing the conditions of claim 13 (Abstract, Page 6 line 18-23). The compounds are used include neurotrophic factors (see full document, specifically Abstract, Page 6 line 12-23, Claim 1-4, 7-10, 13-16).

Hellberg et al. do not expressly teach the use of Rho kinase inhibitors such as fasudil hydrochloride, but does teach the utility of compounds that promote neuron regeneration or neurite outgrowth (neuritogenesis) for treating corneal nerve damage such as the damage from corneal surgery.

McKerracher et al. (WIPO) teaches that Rho antagonists are effective agents for blocking myelin inhibition (e.g. MAG) and stimulate axon growth and neurite outgrowth (both neuritogenesis, Abstract, Page line 10-20, Page 7 line 4-12).

McKerracher also teaches that these Rho inhibitors include Rho kinase inhibitors (Page 7, 11), which are useful for treating conditions and ailments of the peripheral nervous system (PNS) and central nervous system (CNS) by increasing neurite extension, growth, or regeneration (Page 15 line 6-15) . This includes spinal cord injuries and ophthalmic neurons as demonstrated by its application to retinal neurons and crushed optic nerves. The Rho inhibition allowed neurite growth (neuritogenesis). It was also done in the presence of (in combination with) neurotrophic factors (Page 8 line 25-Page 9 line 2, Figure 5 and 7, Page 9 -Page 12, Page 29-34, Claim 22, see full document, specifically areas cited).

McKerracher (Ganglioside) teaches that for damaged nerves, nerve regeneration readily occurs in the peripheral nervous system (PNS) but does not regenerate in the central nervous system (CNS) which is why these injuries are so devastating (Page 7811 first column). McKerracher also teaches that Rho inactivation and inactivation of its downstream agent-Rho kinase, allows long neurite growth as it reverses the

inhibitory ganglioside signaling; making Rho is an important target to overcome growth inhibitors in the nervous system (Figure 1, Page 7812 last column). McKerracher addresses that Rho inhibition or Rho kinase inhibition prevents the growth inhibition of the nerves, and promotes axon regeneration (neuritogenesis) and functional recovery in vivo in spinal cord injury (Page 7812 second column, see full document specifically areas cited).

Hara et al. teaches that fasudil hydrochloride (HA1077) is a known Rho kinase inhibitor that can promote neurological recovery (neuritogenesis) after traumatic spinal cord injury. Hara also addresses that both fasudil and neurotrophic factors (such as those in Hellberg) have neural regeneration properties in the CNS (e.g. spinal cord, Introduction-Page 94, e.g. basic fibroblast growth factor-citation 5, Nerve growth factor-citation 16, 31, 44,) .

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize fasudil hydrochloride to promote neuron regeneration/neurite outgrowth for corneal injury from condition such as corneal surgery, as suggested by McKerracher et al.(WO), McKerracher ,and Hara; and produce the instant invention. It is obvious for one of ordinary skill in the art to use another neurite promoter such as a Rho kinase inhibitor for corneal injury as Hellberg et al. teaches the use of neuron regeneration/neurite outgrowth promoting compounds for treating corneal disorders like corneal nerve damage from surgery, and McKerracher et al.(WO) teaches that Rho inhibitors (i.e. ROCK inhibitors) are also neuron

regenerators/promoters useful for both PNS and CNS conditions like spinal cord injuries and for ophthalmic conditions demonstrated by use for retinal/optic neurons wherein it is obvious to combine the components, each of which is taught by prior art to be useful for neuron regeneration to be used for very same purpose; as it is desirable to have and produce a composition comprising as many components resulting in the additive effect for the neural regeneration.

McKerracher (Ganglioside) addresses that it is known in the art that while neural regeneration occurs in the PNS, it is substantially difficult for it to occur in the CNS as there are inhibitory factors, demonstrating that the CNS is the more difficult environment/embodiment. The combination of Hellberg and McKerracher (WO) for corneal treatment (a PNS area) with Rho/Rho kinase inhibitors has a reasonable expectation of success as the PNS is the more predictable environment, as inhibition of Rho/Rho kinase was shown to be effective in neural regeneration in the CNS (e.g. spinal cord) by McKerracher (Ganglioside) which is the more difficult situation, and is consistent with the teaching of McKerracher et al. (WO) for Rho/Rho kinase inhibitors in both the PNS and CNS.

Hara addresses that fasudil (a known Rho kinase inhibitor) is an effective neuropromoter that recovered injured spinal neurons (spinal cord injury), wherein it *prima facie* obvious to utilize a known Rho kinase neurite/neuron promoter (fasudil) for the neural regeneration in the PNS such as the cornea with Rho kinase inhibitors, as taught by Hellberg and McKerracher with a reasonable expectation of success; as fasudil is a known Rho kinase inhibitor effective for neural regeneration and it is

desirable to use a known Rho kinase inhibitor compound with known regeneration properties for promoting axon extension and regeneration, to treat the same conditions as another neurite/neuron promoters such as neurotrophic factors (e.g. bFGF, NGF) when it is they are both known to be effective to treat neurological damage (e.g. Hara).

Response to Arguments

Applicant's arguments filed 7/5/2011 with respect to claim 13 have been considered but are moot in view of the new ground of rejection.

In regards to the arguments with regards to the declaration and the assertion that the corneal nerve and the optic nerve are different in general, the following aspects are addressed for clarity to expedite prosecution. The declaration by Nakamura and Applicant's arguments are centered on the issue that the trigeminal nerve is different from the optic nerve, and that the references like McKerracher do not teach ROCK inhibitors for the method but are to Rho antagonists like C3 a.

This is fully considered but not persuasive. While the trigeminal nerve is different from the optic nerve, they are both cranial nerves. Additionally, while the corneal nerve which is branched from the trigeminal has motor and sensory aspects, and the optic nerve has sensory; this is not sufficient to show that the actives that promote neural regeneration/outgrowth in the optic nerve as addressed by McKerracher (WO) would not promote neural regeneration/outgrowth in the corneal nerve as McKerracher teaches the Rho/ROCK inhibitors for both the PNS and CNS; as it is well known in the art that all neurons use the same general growth cones to repair/regenerate, and as

addressed by McKerracher (Ganglioside)-it is much harder to have neuron regeneration in the CNS than in the PNS; wherein when the Rho/ROCK inhibition is taught to be useful for both the CNS and PNS, and the examples are to the more difficult embodiment like the optic nerve (CNS), its utility for the PNS like the cornea (which is the less difficult embodiment) has a reasonable expectation of success and the general teaching of McKerracher (WO) is for both PNS and CNS.

In regards to the assertion that McKerracher (WO) does not teach ROCK inhibitors but Rho antagonists like C3, this is not persuasive as McKerracher (WO) does teach Rho kinase inhibitors like Y-27632 (known ROCK inhibitor), and teaches that blocking Rho associated kinase activity (ROCK blocker) is useful for neural regeneration/outgrowth: ROCK inhibitors (see Page 7 and 11). Additionally, the argument the fasudil has other activity in addition to ROCK inhibition is not persuasive as it is also ROCK inhibitor and Hellberg and McKerracher teaches the utility of Rho kinase inhibitors for the method.

There is currently no evidence showing the criticality for the specific claimed compounds for the method over other compounds, or evidence/testing to support the asserted difference for the claimed Rho kinase inhibitors for the optic nerve and the corneal nerve in regards to predictability.

Accordingly, the rejection stands.

Conclusion

8. Claim 13 is rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GIGI HUANG whose telephone number is (571)272-9073. The examiner can normally be reached on Monday-Thursday 8:00AM-6:30PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENIVASAN PADMANABHAN can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GiGi Huang/
Examiner, Art Unit 1627

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627